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(71) Applicant *(for all designated States except US)*: BEECHAM GROUP PLC [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : KING, Francis, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). GREGORY, Julian, Anthony [GB/GB]; 18 Osbourne Street, Moldgreen, Huddersfield HD5 8AY (GB).

(74) Agents: JONES, Pauline et al.; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

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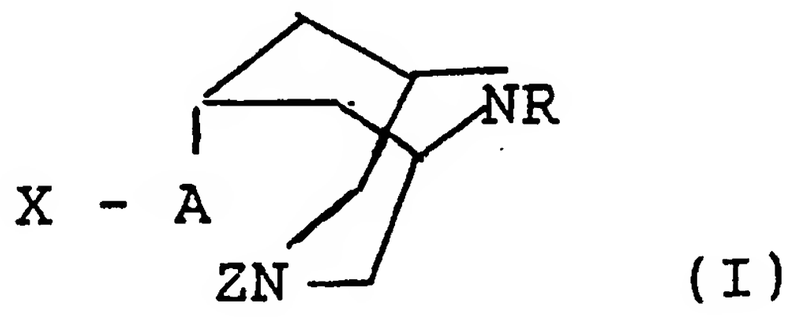
(54) Title: 3,9-DIAZABICYCLO (3.3.1) NONAN-7-YL DERIVATIVES, PROCESS AND INTERMEDIATES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(I)

(57) Abstract

Compounds of formula (I) wherein X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring; A is linking moiety; Z is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl, naphthyl, phenyl C_{1-4} alkyl or naphthyl C_{1-4} alkyl wherein a phenyl or naphthyl moiety is optionally substituted by one or more of halo, C_{1-6} alkoxy or C_{1-6} alkyl; R is hydrogen or methyl having 5-HT_3 receptor antagonist activity.

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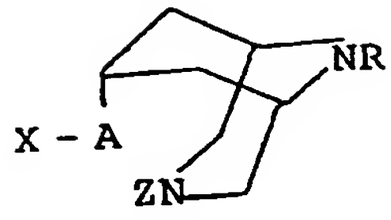
3,9-Diazabicyclo (3.3.1) nonan-7-yl derivatives, process and intermediates for their preparation and pharmaceutical compositions containing them.

This invention relates to novel compounds having pharmacological activity, to a process and intermediates for their preparation, and to their use as pharmaceuticals.

EP-A-158265, EP-A-200444, EP-A-247266, EP-A-235878, EP-A-254584, EP-A-255297, EP-A-289170, EP-A-315390 and PCT/GB91/00636 (Beecham Group p.l.c.), EP-A-158532 (A.H. Robins Company, Inc.), EP-A-67770 (Merrell Toraude et Compagnie), GB 2125398A and GB 2145416A (Sandoz Limited), EP-A-322016 and EP-A-436245 (Duphar international Research B.V.), EP-A-307172 (Eli Lilly and Company), EP-A-323077, EP-A-306148, GB 2208385A and WO91/05738 (John Wyeth and Brother Limited), EP-A-234872 (Adria Laboratories Inc.), EP-A-294292 (Adir et Compagnie), EP-A-339950 (Rorer International (overseas), Inc.), EP-A-309423 (Instituto de Angeli S.p.A.), EP-A-313393 and EP-A-407137 (Yoshitomi Pharmaceutical industries Limited), EP-A-328200 and EP-A-337547 (Merck Sharp and Dohme Limited), EP-A-329932 (Merrell Dow Pharmaceuticals Inc.), WO 90/06039 and WO 91/04738 (Rorer International (Overseas), Inc.), EP-A-378111 (Zambon Group S.p.A.), EP-A-430190 (Syntex (U.S.A.) Inc.) and USA Patents 4920219 and 4920227 (Rorer Pharmaceutical Corp.) disclose classes of compounds which have a saturated azabicyclic moiety, such as tropanyl, granatyl or quinuclidinyl, and are 5-HT_3 receptor antagonists.

A class of novel compounds has now been discovered in which the saturated azabicyclic moiety is **endo**-3,9-diazabicyclo[3.3.1]nonan-7-yl. These compounds have 5-HT_3 receptor antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;

A is a linking moiety;

Z is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl, naphthyl, phenyl C_{1-4} alkyl or naphthyl C_{1-4} alkyl wherein a phenyl or naphthyl moiety is optionally substituted by one or more of halo, C_{1-6} alkoxy or C_{1-6} alkyl;

R is hydrogen or methyl;

having 5-HT_3 receptor antagonist activity.

X may be unsubstituted or substituted, usually by one or more substituents selected from halogen, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl, hydroxy, amino, C_{1-6} alkylamino, C_{1-7} alkanoylamino, or two substituents on X (when fused), may be linked to form a saturated or unsaturated optionally substituted carbocyclic ring.

Heteroatoms for heteroaryl and heterocyclic groups within X are selected from oxygen, nitrogen and sulphur.

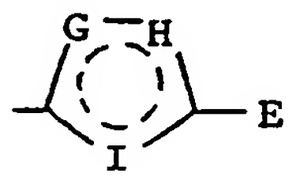
Halo includes bromo, chloro and fluoro.

X may be joined to A by an aromatic carbon atom, or (when X is fused), by a carbocyclic ring carbon atom, or by a heterocyclic ring carbon or nitrogen atom. When X is fused, and A is attached at an aromatic carbon atom, it is preferably attached at the aromatic carbon adjacent a 'fused' carbon atom, which is attached to the heteroatom of a heterocyclic ring in formula (I). The azagranatane side chain may be attached to A in a 'spiro' configuration.

X may also be further joined to A as defined in formula (IA) hereinafter, when $Y-R_{10}$ is N-B=N.

Suitable examples of X are as described in the aforementioned patent publications relating to $5-HT_3$ receptor antagonists, the subject matter of which is incorporated herein by reference.

Suitable examples of A include CONH (amide), COO (ester), NHCONH (ureide), CONHCONH (extended ureide), or a group of structure (j):



(j)

wherein the dotted circle represents two double bonds in any position in the 5 membered ring; two of G, H and I are selected from oxygen, sulphur, nitrogen and carbon and the other is oxygen, sulphur or nitrogen; and E is a bond or C_{1-5} alkylene optionally substituted by phenyl or hydroxy; or E is absent and the heterocycle in structure (j) is joined to the azagranatane, in a 'spiro' configuration, when G is nitrogen, H is methylene and I is oxygen or sulphur.

For the avoidance of doubt, the suitable X values in formula (I) which are described in the referenced patent publications, are that part of the structure remaining when

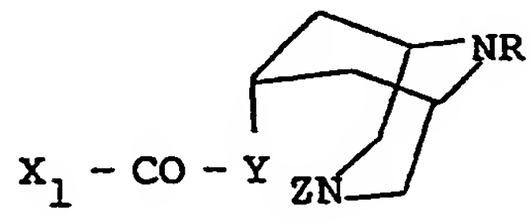
the saturated azabicyclic moiety and A (where A is one of the suitable examples listed above), are disregarded.

Z is often benzyl, n- or iso-butyl, n- or iso-propyl, ethyl or methyl, preferably isopropyl or ethyl.

R is preferably methyl.

There is a group of compounds within formula (I) wherein Z is C_{1-6} alkyl, phenyl or phenyl C_{1-4} alkyl optionally substituted as defined in formula (I).

In a particular aspect, the present invention provides a compound of formula (IA), or a pharmaceutically acceptable salt thereof:

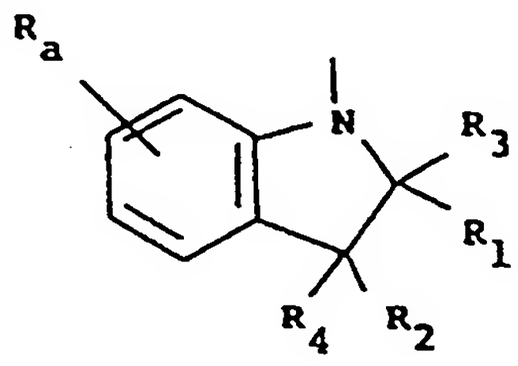


(IA)

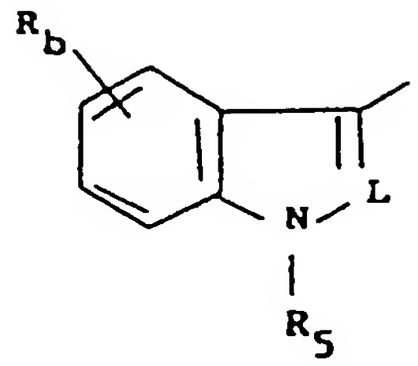
wherein

Y is NH or O (or is joined to R_{10} as defined below);

X_1 is a group of formula (a), (b), (c), (d), (e), (f), or (g) or (h):



(a)



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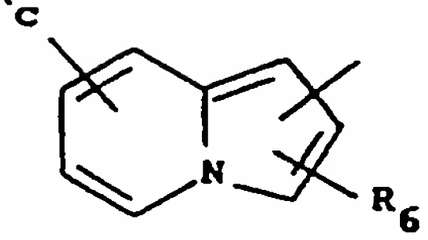
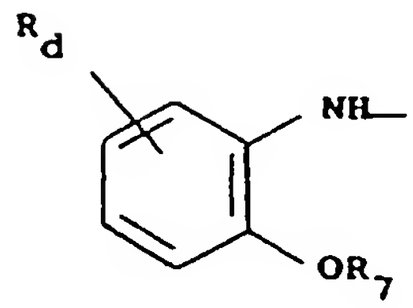


(c)



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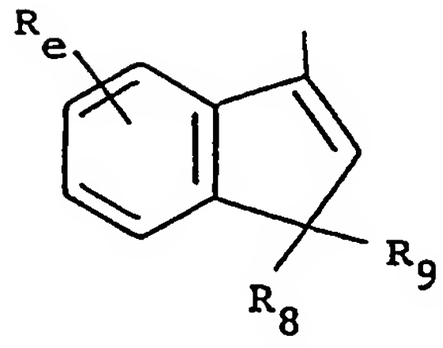
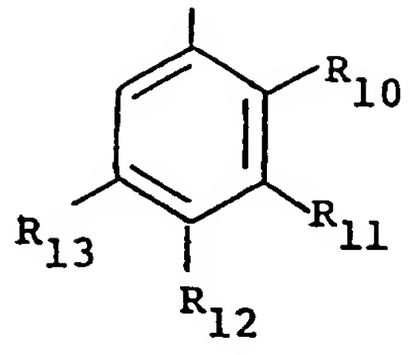
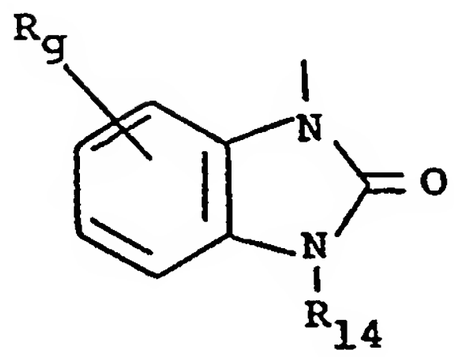


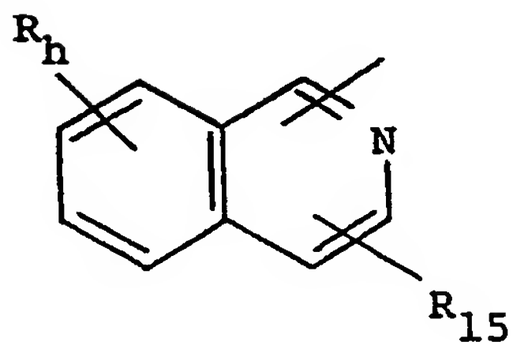
(e)



(f)



(g)



(h)

wherein

R_a to R_e and R_g to R_h are selected from hydrogen, halogen or hydroxy;

R_1 is hydrogen and R_2 is hydrogen or C_{1-4} alkyl; or

R_1 and R_2 together are a bond;

R_3 to R_7 are independently hydrogen or C_{1-6} alkyl; and

R_4 together with R_2 may be C_{2-7} polymethylene or C_{2-6} polymethylene interrupted by an -O- linkage when R_1 is hydrogen;

R_8 and R_9 are independently selected from hydrogen or C_{1-6} alkyl or R_8 and R_9 together are C_{2-6} polymethylene or C_{2-5} polymethylene interrupted by an -O- linkage;

either R_{10} is hydrogen, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy or C_{3-8} cycloalkyl C_{1-4} alkyloxy; or R_{10} is joined to Y so that Y-R_{10} is N-B=N where B is N or CH; and

R_{11} is hydrogen, halo, C_{1-6} alkoxy or C_{1-6} alkyl; or

R_{10} and R_{11} are joined to form -OCH($R_{15}R_{16}$)-E- wherein E is $(CH_2)_n$ or $NR_{17}CO(CH_2)m$ wherein n is 1 or 2 and m is 0 or 1 and R_{15}, R_{16} and R_{17} are independently selected from hydrogen or C_{1-6} alkyl;

R_{12} is hydrogen, C_{1-6} alkoxy or; amino optionally substituted by a C_{1-6} alkyl group, or R_{12} is alkanoylamino; and

R_{13} is halo, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio;

R_{14} is hydrogen or C_{1-6} alkyl;

in formula (h):

CO-Y- is in the 1-position and either R_{15} is in the 3-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, phenyl optionally substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups or by C_{4-5} polymethylene or by phenyl, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy or nitro; or

CO-Y- is in the 3-position and either R_{15} is in the 1-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen or C_{1-6} alkoxy;

L is CH or N; and

Z and R are as defined in formula (I).

Examples of moieties in alkyl or alkyl containing groups in Z or in R_1 to R_{15} include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, preferably methyl. Cycloalkyl moieties include C_3, C_4, C_5, C_6, C_7 and C_8 cycloalkyl. Halo moieties include fluoro, chloro, bromo and iodo.

Suitable examples of R_2 and R_4 or R_8 and R_9 when joined include C_2, C_3, C_4, C_5 or C_6 polymethylene, preferably C_2, C_3, C_4 or C_5 polymethylene.

R_a to R_e and R_g to R_h are preferably selected from hydrogen, fluoro, chloro and hydroxy, most preferably hydrogen. R_b may be 5-, 6- or 7-chloro or fluoro.

When X is of sub-formula (a), one of R_1 and R_3 is preferably hydrogen and one or both of R_2 and R_4 (most preferably both) are alkyl groups, such as methyl, or are joined to form C_{2-7} polymethylene; or when one of R_2 and R_4 is hydrogen, the other is preferably ethyl or n- or iso- propyl.

When X is of sub-formula (b), R_5 is preferably hydrogen or a methyl or ethyl group.

When X is of sub-formula (c), one of CO-Y and R_6 is attached at the 1-position and the other is attached at the 3-position as depicted in sub-formula (c), and R_6 is preferably methyl or ethyl.

When X is of sub-formula (d), R_7 is preferably methyl.

When X is of sub-formula (e), R_8 and R_9 are preferably both methyl groups.

When X is of sub-formula (f), and R_{10} is C_{1-6} alkoxy or is joined to Y, R_{12} is preferably amino and R_{13} is preferably chloro or bromo, most preferably chloro. R_{10} is preferably methoxy when C_{1-6} alkoxy.

When X is of sub-formula (f), and R_{10} is hydrogen, R_9 and R_{11} are preferably chloro or methyl and R_{10} is preferably hydrogen.

Other values of X within sub-formula (f) of interest are those described in EP-A-307172 (Eli Lilly and Company) and EP-A-313393 (Yoshitomi Pharmaceutical Industries Limited).

When X is of sub-formula (g), R_{14} is preferably hydrogen or methyl.

When X is of sub-formula (h), and CO-Y- is in the 1-position suitable examples of R_{15} when in the 4-position, include the following: hydrogen, chloro, bromo, methyl, ethyl, amino, methylamino, dimethylamino, phenyl, C_{1-4} alkanoylamino such as formylamino, acetylamino, propionylamino, n- and iso-butyrylamino, aminosulphonyl, and amino and aminosulphonyl optionally substituted by one or two methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl or phenyl groups; nitro, n- and iso-propoxy, methylthio, ethylthio, n- and iso-propylthio, hydroxy, methylsulphonyl and ethylsulphonyl or when R_{15} is in the 3-position suitable examples, include the following groups, hydrogen, methyl, ethyl, n- or iso-propyl, methoxy, and ethoxy.

When X is at sub-formula (h), and the CO-Y- is in the 3-position, suitable examples of R_{15} when in the 1-position, include hydrogen, methyl, ethyl, n- or iso- propyl, or when R_{15} is in the 4-position, suitable examples include the following: hydrogen, methoxy and ethoxy.

Preferred R_{15} groups, in any of the positions specified above, include hydrogen, methyl and methoxy. CO-Y- is preferably in the 1-position.

Y is preferably NH.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

Preferably the acid addition salt is the hydrochloride salt.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

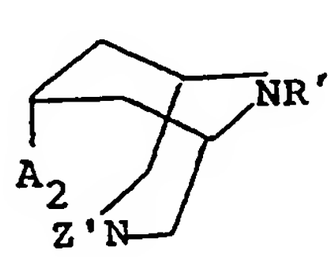
Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

It will be appreciated that mono- or di- salts may be formed owing to the presence of two salifiable nitrogens in the azagranatane side chain.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

The invention also provides a process for the preparation of a compound of formula (I) which process comprises reacting a compound $X'-A_1$ with a compound of formula (II):



(II)

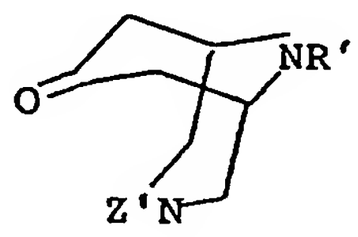
wherein A_1 and A_2 are moieties which react together, usually by an amide or ester coupling, or by condensation to form a

heterocycle (j) as hereinbefore defined, to form A as defined; X′ is X or a group convertible thereto and R′ and Z′ are R and Z as defined or a hydrogenolysable protecting group; and thereafter as desired or necessary, converting X′ to X, converting R′/Z′, when other than R/Z, to R/Z, and optionally forming a pharmaceutically acceptable salt of the compound of formula (I).

Suitable values of A_1 and A_2 are as described in the aforementioned patent publications.

Intermediates of the formula X′-A_1 are generally known from the aforementioned patent publications/references, or are prepared by analogous methods to those used for structurally related known compounds.

Intermediates of the formula (II) are generally prepared from the compound of formula (III):

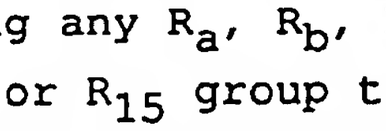


(III)

which is prepared by the condensation/cyclisation of as appropriate 2,6-disubstituted piperazine derivative, as described in the descriptions hereinafter.

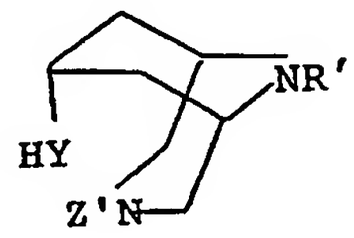
In a particular aspect, the invention also provides a process for the preparation of a compound of formula (IA),

or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (IV):



(IV)

with a compound of formula (V):



(V)

or a reactive derivative thereof, when Y is O;

wherein X_1' is X_1 or a group convertible thereto; Q_1 is a leaving group; R' is R as defined, or a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting X_1' to X_1, including any R_a, R_b, R_c, R_d, R_e, R_g, R_h or R_{10}, R_{11}, R_{12}, R_{13}, R_{14} or R_{15} group to another such group, converting R'/Z', when other than R/Z, to R/Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (IA).

Examples of leaving groups Q_1, displaceable by a nucleophile, include halogen such as chloro and bromo, C_{1-4} alkoxy, such as CH_3O and C_2H_5O-, PhO-, or activated hydrocarbyloxy, such as Cl_5C_6O- or Cl_3CO-

If a group Q_1 is a halide, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or

dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0°-100°C, in particular 10-80°C are suitable.

If a group Q_1 is C_{1-4} alkoxy, phenoxy or activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as toluene ordimethylformamide. It is also preferred that the group Q_1 is Cl_3CO- and that the reaction is carried out in toluene at reflux temperature.

When Y is O the compound of formula (V) may be in the form of a reactive derivative thereof, which is often a salt, such as the lithium, sodium or potassium salt.

Usually, X_1' will be X_1, but when R_{10} is joined to Y, in formula (IA), X_1' is of sub-formula (f) wherein R_{10} is nitro or amino, which may be subsequently be linked to Y as described in EP-A-315390.

It will be apparent that compounds of the formula (IA) containing an R_a to R_e, R_g, R_h or R_{10} to R_{15} group which is convertible to another such group are useful novel intermediates. i.e. a hydrogen substituent is convertible to a halogen substituent by halogenation using conventional halogenating agents; or a C_{1-7} alkanoylamino substituent is convertible to amino by conventional hydrolysis.

R'/Z' when other than R/Z may be a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups selected from halo, C_{1-4} alkoxy and C_{1-4}

alkyl. Such benzyl groups may, for example, be removed, when R_a to R_e, R_g, R_h, R_{11} to R_{15} is not halogen, by conventional transition metal catalysed hydrogenolysis to give the corresponding compound wherein R'/Z' is hydrogen.

A further process for the preparation of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, therefore comprises N-alkylating a compound of formula (I), wherein R/Z is hydrogen and optionally forming a pharmaceutically acceptable salt of the resulting compound of the formula (I). In this further process of the invention 'N-alkylation' comprises the substitution of the azabicyclic N-atoms by a group R/Z as hereinbefore defined. This may be achieved by reaction with a compound RQ_3 or ZQ_3 wherein R and Z are as hereinbefore defined and Q_3 is a leaving group. Suitable values for Q_3 include groups displaced by nucleophiles such as Cl, Br, I, OSO_2CH_3 or $OSO_2C_6H_4pCH_3$. Favoured values for Q_3 include Cl, Br and I. The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slightly above. Alternatively, 'N-alkylation' may be effected under conventional reductive alkylation conditions.

Interconverting R or Z in the compound of the formula (V) before coupling with the compound of the formula (IV) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C_{2-7} alkanoyl group, before R/Z interconversion.

It is often convenient in the preparation of such a compound of formula (V) to prepare the corresponding compound wherein

the methylene group is replaced by -CO-, or for R or Z is methyl, where the methyl group is replaced by alkoxycarbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (IV).

The compounds of formula (IV) are known or are preparable analogously to, or routinely from, known compounds.

Compounds of the formula (V) wherein R′ is R and Z′ is Z as defined, are novel and form an aspect of the invention.

Compounds of the formula (I) may also be prepared by the processes analogous to those described in the aforementioned European Patent Publications.

It will be realised that in the compound of the formula (I) the -A- linkage has an **endo** orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of **endo** and **exo** isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the **endo** isomer may if desired by synthesised from the corresponding **endo** form of the compound of the formula (II).

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally.

The salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are $5\text{-}HT_3$ receptor antagonists and it is thus believed may generally be used in

the treatment or prophylaxis of pain, emesis, CNS disorders and gastrointestinal disorders. Pain includes migraine, cluster headache, trigeminal neuralgia and visceral pain; emesis includes, in particular, that of preventing vomiting and nausea associated with cancer therapy, post-operative emesis, and nausea associated with migraine. Examples of such cancer therapy include that using cytotoxic agents, such as platinum complexes including cisplatin, and also doxorubicin and cyclophosphamide, particularly cisplatin; and also radiation treatment. CNS disorders include anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory impairment (AAMI), and drug dependence. Gastrointestinal disorders include irritable bowel syndrome and diarrohea.

5-HT_3 receptor antagonists may also be of potential use in the treatment of obesity and/or arrhythmia.

Some of the compounds of the invention may also have gastric prokinetic activity, useful in the treatment of gastrointestinal disorders, for example when R_{14} is C_{1-6} alkyl.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such

liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which

comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

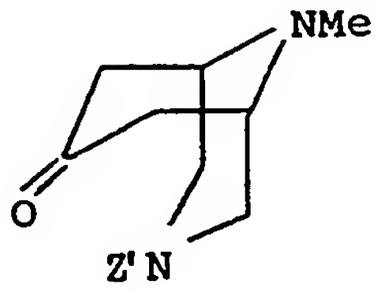
No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

The invention also provides a pharmaceutical composition for use in the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders which composition comprises an effect non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carrier.

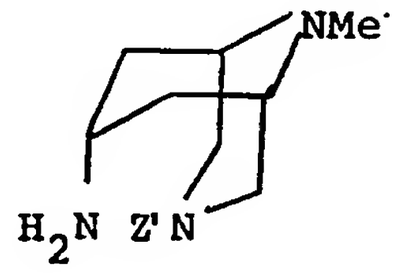
The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

The following Examples illustrate the preparation of compounds of formula (I); the following descriptions illustrate the preparation of intermediates.

Intermediates of formulae (III)' and (V)'



(III)'



(V)'

	Z'
D1c/d*	CH_2Ph
D2c/d	CH_2Ph
D3c/d	^{i}Pr
D4c/d	^{n}Pr
D5c/d	^{i}Bu
D6c/d	^{n}Bu
D7c/d	Ph
D8c/d	Nm
D9c/d	Me
D10c/d	Et
D11c/d	Pe
D12c/d	Cm

Nm = 1-naphthylmethyl;
Cm = cyclohexylmethyl;
Pe = phenethyl

* mixture of **endo** and **exo** isomers

Description 1

3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine

a) Ethyl 4-bromocrotonate (25g) in Et_2O (200 ml) was stirred, cooled to 0°C and benzylamine (12.6ml) in Et_2O (50ml) was added dropwise. The reaction was stirred at room temperature for 2 days, filtered and the filtrate washed with H_2O, dried (Na_2SO_4) and concentrated. Column chromatography of the residue on silica, eluting with 1:3 Et_2O:petrol gave diethyl-4,4^1-benzylimino di-trans-2-butenoate (15g).

b) The above diester (29g) dissolved in MeOH (300ml) at 0°C was treated with solution of 33% $MeNH_2$ in IMS (5.7ml). The reaction mixture was stirred at room temperature overnight, the solvent removed and the residue filtered through silica, eluting with 1:1 Et_2O:petrol to give dimethyl-4-benzyl-1-methyl-piperazinyl-2,6-diacetate (D1b) (13.9g).

c) The diester (13.9g) in toluene (150 ml) was added dropwise during 1h to a stirred suspension of Bu^tOK (12.9g) in toluene (600ml) being heated to reflux. After heating for a further 30 min., no starting material remained as determined by TLC. On cooling, the intermediate β-keto ester was extracted into 5N HCl (200ml) and the acidic extract heated to vigorous reflux for 5h. The reaction mixture was concentrated and the residue neutralised, then saturated with K_2CO_3 and the product extracted into $CHCl_3$. The concentrated organic extracts were purified by column chromatography on silica, eluting with 5% MeOH/$CHCl_3$ to give 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D1c) (3.7g).

d) The ketone (D1c)(2g) in EtOH (50ml) was heated to reflux with $H_2NOH.HCl$ (0.65g) for 1h. The reaction mixture

was cooled, concentrated to approx. 1/3rd volume, treated with a little ether and the hydrochloride salt of the oxime collected and dried (1.7g). The oxime hydrochloride (0.9g) was reduced with sodium (1.2g) in amyl alcohol (50ml) at reflux. After all the sodium had dissolved, the mixture was cooled to 90°C, water (4ml) was carefully added, then allowed to re-cool to room temperature. The aqueous layer was separated and the amyl alcohol extracted with an excess of 5N HCl. Concentration of the acidic extract, neutralisation then saturation with K_2CO_3 and extraction of the product into $CHCl_3$ gave, on concentration, the title compounds (D1d) (0.64g) as a crude mixture of **endo** and **exo** isomers.

Description 2

endo-3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine

a) To methyl-4-bromocrotonate (50g) in diethyl ether (500ml) was added, dropwise benzylamine (22ml) in diethyl ether (20ml) at 0°C. The reaction mixture was stirred at room temperature for 72h. The precipitate was removed by filtration and the filtrate washed with water (75 ml). The organic phase was dried ($MgSO_4$), the solvent evaporated under reduced pressure and the residue purified using flash chromatography on silica eluting with light petrol and diethyl ether to afford dimethyl-4,4^1-benzyliminodi-**trans**-2-butenoate (17.1g).

b) To dimethyl-4,4^1-benzyliminodi-**trans**-2-butenoate (17.1g) in methanol (250 ml) was added dropwise methylamine (7.5 ml, 33% w/w in IMS) at 0°C. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue chromatographed on silica using light petrol and diethyl ether as the eluant to afford dimethyl-1-benzyl-4-methyl

piperazinyl-3,5-diacetate as a mixture of **cis** and **trans** isomers (9.29g).

c) To potassium tert-butoxide (9.67g) in toluene (350 ml) was added dimethyl-4-benzyl-1-methyl piperazinyl-2,6-diacetate (9.26g) in toluene (150 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was heated to reflux for 3h. The reaction mixture was cooled and washed with 5N HCl (4x75ml). The combined aqueous extracts were heated to reflux for 13h. The reaction mixture was cooled, the solvent concentrated under reduced pressure and the residue saturated with solid potassium carbonate. The product was extracted into chloroform (4x75ml), the organic phase dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Flash chromatography on silica using chloroform with increasing volumes of ethanol (up to 10%) eluant gave 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D2c) (1.8g).

d) To a stirred solution of the above ketone (1.80g) in ethanol (50ml) was added hydroxylamine hydrochloride (0.54g). The reaction mixture was then heated to reflux for 2h. The reaction mixture was cooled and the solvent evaporated under reduced pressure. The residue was triturated with diethyl ether to give 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one oxime hydrochloride (1.87g).

To a stirred solution of alane [generated by the action of conc. H_2SO_4 (0.93ml) on lithium aluminium hydride (0.88g) in dry THF (30ml)] was added 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one oxime [generated by the treatment of 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one oxime hydrochloride with potassium carbonate). The reaction mixture was then heated to reflux overnight under a nitrogen atmosphere. The reaction mixture was cooled and 40% aqueous NaOH solution (2ml) and water (1ml) were added dropwise. Diethyl ether (5ml) was added and the mixture

stirred for 1h. The resultant precipitate was removed by filtration through keiselguhr and the filtrate concentrated under reduced pressure to afford the crude title compound (D2d) (0.90g).

Following the procedures outlined in Descriptions 1 and 2, parts a) to c) the following intermediates were obtained:

3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D3c);

3-n-propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D4c);

3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D5c);

3-^{n}butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D6c);

9-methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D7c);

9-methyl-3-(1-naphthylmethyl)-3,9-diazabicyclo[3.3.1]nonan-7-one (D8c);

3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D9c);

3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D10c);

9-methyl-3-(2-phenethyl)-3,9-diazabicyclo[3.3.1]nonan-7-one (D11c);

3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one (D12c).

Following the procedures outlined in descriptions 1d) and 2d) the following intermediates were obtained:

endo-3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D3d);

endo-3-^{n}propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D4d);

endo-3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D5d);

endo-3-^{n}butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D6d);

endo-9-methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D7d);

endo-9-methyl-3-(1-naphthylmethyl)-3,9-diazabicyclo[3.3.1]-nonan-7-amine (D8d);

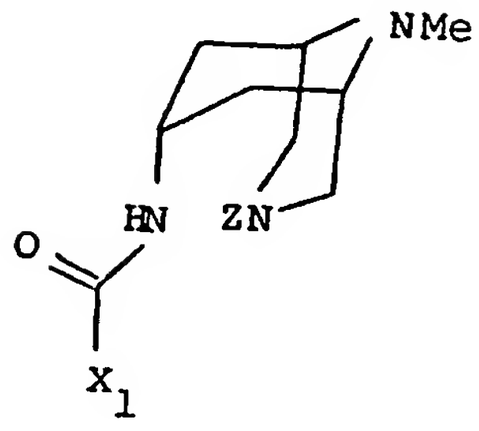
exo/endo-3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D9d);

endo-3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D10d);

endo-9-methyl-3-(2-phenethyl)-3,9-diazabicyclo[3.3.1]-nonan-7-amine (D11d);

endo-3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]-nonan-7-amine (D12d);

Examples



	X_1	Z
E1a/ E1b	X_1 = (f): R_{10} = OCH_3, R_{11} = H, R_{12} = $NHCOCH_3$, NH_2, R_{13} = Cl.	CH_2Ph
E2	(as E1b)	Me
E3	X_1 = (b): L = N, R_5 = CH_3, R_b = H.	CH_2Ph
E4	(as E3)	^iPr
E5	(as E3)	^nPr
E6	(as E3)	^iBu
E7	(as E3)	^nBu
E8	(as E3)	Ph

	X_1	Z
E9	(as E3)	Nm
E10	(as E3)	Et
E11	(as E3)	Pe
E12	(as E3)	Cm
E13	X_1 = (a): R_1 = H, R_2 = Me, R_3 = H, R_4 = Me, R_a = H.	CH_2Ph
E14	(as E13)	^{i}Pr
E15	(as E13)	Me
E16	(as E13)	Et
E17	(as E13)	^{n}Pr
E18	(as E13)	^{n}Bu
E19	(as E13)	^{i}Bu
E20	(as E13)	Cm
E21	(as E13)	H

Example 1

endo-4-Acetylamino-5-chloro-2-methoxy-N-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)benzamide (E1a)

A solution of the crude amine (D1d) (0.64g) and Et_3N (0.4ml) in CH_2Cl_2 (20ml) was added to a stirred solution of 4-acetylamino-5-chloro-2-methoxybenzoyl chloride (0.75g) in CH_2Cl_2 (50ml) at 0°C. After stirring overnight the reaction mixture was washed with aqueous $NaHCO_3$, dried, filtered and concentrated. The residue was purified by column chromatography on alumina, eluting with 1:1 $CHCl_3$:petrol to give three fractions;

Fraction 1; 0.24g **exo** isomer

Fraction 2; 0.46g mixture of **endo/exo** isomers

Fraction 3; 0.23g **endo** isomer (mainly) compound E1.

endo-4-Amino-5-chloro-2-methoxy-N-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)benzamide (E1b)

The mainly **endo** isomer (E1a), (fraction 3) (0.23g) was hydrolysed with 10% NaOH solution (1.0ml) in EtOH (20ml) and H_2O (5ml) heated for 2 hours. The solvent was removed and the residue extracted into $CHCl_3$. The organic extract was dried and concentrated. The residue was filtered through alumina, eluting with $CHCl_3$ to give the desired product E2 (0.12g) mp 145-162°C which contained ca. 20% of the **exo** isomer.

MS M^+ 428, 430

^1H NMR ($CDCl_3$); δ: 9.8 (brd 1H), 8.15 (s, 0.2H), 7.7 (s, 0.8H), 7. 5-6.8 (m, 5H), 6.29 (s, 0.2H), 6.21 (s, 0.8H), 5.7-5.5 (m, 0.2H), 4.65-4.5 (m, 0.8H),4.35 (brs, 0.4H), 4.24 (brs, 1.6H), .86 (s, 0.6H), 3.78 (s 2.4H), 3.5 (s, 2H), 3.0-2.3 (m 9H including 2.5, s, 3H), 1.42 (3, 1.6H).

Example 2

endo-4-Amino-5-chloro-2-methoxy-N-(3,9-dimethyl-3,9-diazabicyclo-[3.3.1]nonan-7-yl)benzamide (E2)

The title compound was prepared in a similar manner to that described in Example 1, from 3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D9d).

Example 3

endo-N-1-Methyl-3-indazolyl-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E3)

To a stirred suspension of 1-methyl-1H-indazole-3-carboxylic acid (0.50g) in CH_2Cl_2 (40ml) was added oxalyl chloride (0.25ml) and 3 drops of DMF. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated under reduced pressure to afford crude 1-methyl-1H-indazole-3-carbonyl chloride.

To a solution of 1-methyl-1H-indazole-3-carbonyl chloride (127 mg) in CH_2Cl_2 (20ml) was added a solution of **endo**-3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D2d) (160 mg) and triethylamine (90µl) in CH_2Cl_2 (5ml). The reaction mixture was stirred overnight at room temperature. The resulting solution was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and the solvent removed under reduced pressure to afford crude product. Flash chromatography on silica using chloroform and ethanol as the eluant gave the title compound (E3) (33mg) mp 173-176°.

^1H NMR (CD_3OD) 400 MHz; δ: 1.51 (d, 2H), 2.48 (s, 3H), 2.51-2.60 (m, 2H), 2.63 (dd, 2H), 2.80 (d, 2H), 2.87-2.92 (m,

2H), 3.92 (s, 5H), 4.50-4.59 (m, 1H), 7.09-7.18 (m, 3H), 7.29 (t, 1H), 7.35 (d, 2H), 7.47 (t, 1H), 7.57 (d, 2H), 8.22 (d, 1H).

M^+ 403

Examples 4-12

Following the general procedure outlined in Example 3, the following compounds were obtained:

endo-N-1-Methyl-3-indazolyl-(3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E4)

mp 180-184°C

^1H NMR ($CDCl_3$) 250 MHz; δ: 1.27 (d, 6H), 1.49 (d, 2H), 2.45-2.59 (m, 5H), 2.65-2.81 (m, 3H), 2.85 (d, 2H), 4.08 (s, 3H), 4.63-4.77 (m, 1H), 7.22-7.30 (m, 1H), 7.36-7.47 (m, 2H), 8.42 (d, 1H), 10.62 (d, 1H).

M^+ 355

endo-N-1-Methyl-3-indazolyl-(9-methyl-3-^{n}propyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E5)

mp 147-149°C

^1H NMR ($CDCl_3$) 250MHz; δ: 0.97 (t, 3H), 1.50 (d, 2H), 1.70-1.88 (m, 2H), 2.43-2.63 (m, 2H), 2.81-2.96 (m, 4H), 4.07 (s, 3H), 4.63-4.77 (m, 1H), 7.23-7.31 (m, 1H), 7.35-7.48 (m, 2H), 8.41 (d, 1H), 10.70 (d, 1H).

M^+ 355

endo-N-1-Methyl-3-indazolyl-(3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E6)

mp 107-109°C

^{1}H NMR ($CDCl_3$) 250 MHz; δ:0.89 (d, 6H), 1.58 (d, 2H), 1.95-2.10 (m, 1H), 2.40-2.74 (m, 9H), 2.87 (d, 2H), 2.92-3.05 (m, 2H), 4.09 (s, 3H), 4.68-4.81 (m, 1H), 7.23-7.31 (m, 1H), 7.38-7.48 (m, 2H), 8.34 (d, 1H), 10.25 (d, 1H).

MH^+ 370

endo-N-1-Methyl-3-indazolyl-(3-^{n}butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E7)

mp 91-93°C

^{1}H NMR ($CDCl_3$) 250 MHz; δ: 0.93 (t, 3H), 1.30-1.44 (m, 2H), 1.52 (d, 2H), 1.62-1.78 (m, 2H), 2.47-2.68 (m, 9H), 2.88 (d, 2H), 2.91-2.99 (m, 2H), 4.06 (s, 3H), 4.65-4.78 (m, 1H), 7.22-7.30 (m, 1H), 35-7.47 (m, 2H), 8.41 (d, 1H), 10.67 (d, 1H).

MH^+ 370

endo-N-1-Methyl-3-indazolyl-(9-methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E8)

mp 131-134°C

^{1}H NMR ($CDCl_3$) 250Hz; δ: 1.69 (d, 2H), 2.61 (s, 3H), 3.11-3.21 (m, 2H), 3.23-3.34 (m, 2H), 3.39 (s, 3H), 3.43-3.60 (m, 4H), 4.69-4.72 (m, 1H), 6.98 (t, 1H), 7.08 (d, 2H), 7.15-7.41 (m, 5H), 8.31 (d, 1H), 9.45 (d, 1H).

M^+ 389

endo-N-1-Methyl-3-indazolyl-(3-(1-naphthylmethyl)-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E9)

MP 89-92°C

^{1}H NMR ($CDCl_3$) 250 MHz; δ: 1.55 (d, 2H), 2.44-2.61 (m, 5H), 2.71-2.82 (m, 2H), 2.83-3.00 (m, 4H), 3.68 (s, 3H), 4.45 (s, 2H), 4.68-4.79 (m, 1H), 7.17 (t, 1H), 7.24-7.53 (m, 5H), 7.64 (d, 1H), 7.71 (d, 1H), 7.82-7.91 (m, 1H), 8.20-8.28 (m, 1H), 8.43 (d, 1H), 10.87 (d, 1H).

MH^+ 454

endo-N-1-Methyl-3-indazolyl-(3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E10)

mp 140-143°C

^{1}H NMR ($CDCl_3$) 250 MHz; δ: 1.30 (t, 3H), 1.52 (d, 2H), 2.45-2.70 (m, 9H), 2.85 (d, 2H), 2.95 (brs, 2H), 4.08 (s, 3H), 4.60-4.75 (m, H), 7.20-7.30 (m, H), 7.35-7.46 (m, 2H), 8.42 (d, H), 10.85 (d, H).

MS M^+ = 341

endo-N-1-Methyl-3-indazolyl-(9-methyl-3-phenethyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E11)

mp 129-131°

^{1}H NMR ($CDCl_3$) 250 MHz; δ: 1.57 (d, 2H), 2.50-2.68 (m, 5H), 2.70-2.84 (m, 2H), 2.85-3.05 (m, 6H), 3.06-3.18 (m, 2H), 3.80 (s, 3H), 4.68-4.80 (m, H), 7.15-7.48 (m, 8H), 8.40 (d, H), 10.56 (d, H).

MS M^+ = 417

endo-N-1-Methyl-3-indazolyl-(3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E12)

mp 82-85°C

^{1}H NMR ($CDCl_3$) 250 MHz; δ: 0.75-1.15 (m, 4H), 1.40-1.72 (m, 8H), 2.45 (d, 2H), 2.48-2.72 (m, 7H), 2.80 (d, 2H), 2.94 (brs, 2H), 4.10 (s, 3H), 4.62-4.79 (m, H), 7.20-7.32 (m, 2H), 7.35-7.48 (m, 2H), 8.32 (d, H), 10.21 (d, H).

MS (E1) M^+ = 409

Example 13

endo-N-3,3-Dimethylindolin-1-yl(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E13)

A solution of 3,3-dimethylindoline (1.5g) and triethylamine (1.42ml) in CH_2Cl_2 (15ml) was added dropwise to a cooled stirred solution of phosgene (9ml, 12.5% w/w in toluene) in CH_2Cl_2 (15ml). The reaction mixture was stirred for 1h at 0°C and then poured into pentane (100ml), washed with 5N sulphuric acid (5ml) and brine (5ml). The organic phase was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give crude 1-(2,3-dihydro-3,3-dimethyl)indolylcarbonyl chloride (1.7g).

To a stirred solution of 1-(2,3-dihydro-3,3-dimethyl)indolylcarbonyl chloride (771mg) in CH_2Cl_2 (15ml) at ambient temperature was added endo-3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine (D2d) (902mg) and triethylamine (512µl) in CH_2Cl_2 (15ml). The reaction mixture was stirred at room temperature overnight. The resulting solution was washed with aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and the solvent removed by rotary evaporation.

Flash chromatography on silica using chloroform and ethanol as the eluant gave the title compound (E13) (360mg) mp 188-191°C.

^{1}H NMR ($CDCl_3$) 250MHz; δ: 1.29 (s, 6H), 1.48 (d, 2H), 2.40-2.57 (m, 5H), 2.62-2.78 (m, 4H), 2.83-2.90 (m, 2H), 3.53 (s, 2H), 3.70 (s, 2H), 4.39-4.42 (m, 1H), 6.90 (t, 1H), 7.05-7.46 (m, 8H), 7.81 (d, 1H), 8.78 (d, 1H).

Examples 14-20

Following the general procedure outlined in Example 13, the following compounds were obtained; in the case of hydrochloride salts, by treatment of the free base with ethereal HCl.

endo-N-3,3-Dimethylindolin-1-yl(3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E14)

mp 109-111°C

^{1}H NMR ($CDCl_3$) 250MHz; δ: 1.05 (d, 6H), 1.33 (s, 6H), 1.47 (d, 2H), 2.41-2.75 (m, 10H), 2.88-2.96 (m, 2H), 3.65 (s, 2H), 4.24-4.38 (m, 1H), 6.90 (t, 1H), 7.06-7.19 (m, 2H), 7.80 (d, 1H), 8.58 (d, 1H).

MH^+ 371

endo-N-3,3-Dimethylindolin-1-yl(3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E15)

mp 173-175°

^{1}H NMR ($CDCl_3$) 400 MHz; δ: 1.34 (s, 6H), 1.45 (d, 2H), 2.31 (s, 3H), 2.40-2.50 (m, 2H), 2.52 (s, 3H), 2.55-2.65 (m, 2H), 2.69 (d, 2H), 2.88 (brs, 2H), 3.54 (s, 2H), 4.25-4.36 (m,

H), 6.90 (t, H), 7.07 (d, H), 7.15 (t, H), 7.93 (d, H), 9.15 (d, H).

MS M^+=342

endo-N-3,3-Dimethylindolin-1-yl(3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E16)

mp 150°

^1H NMR ($CDCl_3$) 250 MHz; δ: 1.05 (t, 3H), 1.35 (s, 6H), 1.46 (d, 2H), 2.40-2.60 (m, 9H), 2.75 (d, 2H), 2.90 (brs, 2H), 3.60 (s, 2H), 4.25-4.40 (m, H), 6.90 (t, H), 7.05-7.20 (m, 2H), 7.85 (d, H), 8.95 (d, H).

MS MH^+ = 357

endo-N-3,3-Dimethylindolin-1-yl(3-^{n}propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide hydrochloride (E17)

mp 139-142°C

^{1}HNMR ($CDCl_3$) 250 MHz - Free base; δ: 0.80 (t, 3H), 1.32 (s, 6H), 1.45 (d, 2H), 1.62-1.79 (m, 2H), 2.26-2.46 (m, 2H), 2.47-2.57 (m, 7H), 2.74 (d, 2H), 2.82-2.89 (m, 2H), 3.58 (s, 2H), 4.21-4.33 (m, 1H), 6.89 (t, 1H), 7.01-7.19 (m, 2H), 7.89 (d, 1H), 9.02 (d, 1H).

MH+ 371 (Free base)

endo-N-3,3-Dimethylindolin-1-yl(3-^{n}butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide hydrochloride (E18)

mp 135-138°C

^{1}H NMR ($CDCl_3$) 250 MHz - Free base; δ: 0.85 (t, 3H), 1.15-1.52 (m, 12H), 2.30-2.56 (m, 9H), 2.76 (d, 2H), 2.83-2.92 (m, 2H), 3.59 (s, 2H), 4.23-4.37 (m, 1H), 6.60 (t, 1H), 7.06-7.20 (m, 2H), 7.80 (d, 1H), 9.00 (d, 1H).

MH^+ 385 (Free base)

endo-N-3,3-Dimethylindolin-1-yl(3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide hydrochloride (E19)

mp 141-144°C

^{1}H NMR ($CDCl_3$) 250MHz (Free base); δ: 0.69 (d, 6H), 1.30 (s, 6H), 1.49 (d, 2H), 2.17 (d, 2H), 2.39-2.55 (m, 8H), 2.65-2.78 (m, 2H), 2.81-2.90 (m, 2H), 3.64 (s, 2H), 4.25-4.37 (m, 1H), 6.88 (t, 1H), 6.98-7.15 (d, 1H), 7.51 (d, 1H), 8.69 (d, 1H).

MH^+ 385 (Free base)

endo-N-3,3-Dimethylindolin-1-yl(3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl carboxamide hydrochloride (E20)

mp 130°C

^{1}H NMR ($CDCl_3$) 250 MHz; δ: 0.55-0.80 (m, 2H), 0.85-1.38 (m, 8H, including 1.33 (s, 6H), 1.40-1.90 (m, 10H), 2.22 (d, 2H), 2.40-2.59 (m, 7H including 2.50 (s, 3H)), 2.74 (d, 2H),

2.85 (brs, 2H), 3.65 (s, 2H), 4.29-4.43 (m, H), 6.90 (t, H), 7.05-7.19 (m, 2H), 7.62 (d, H).

MS M^+ = 425

Example 21

endo-N-3,3-Dimethylindolin-1-yl-(9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E21)

endo-N-3,3-Dimethylindolin-1-yl(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide (E13) (350 mg) was hydrogenated at atmospheric pressure in methanol (50ml) over 5% Pd/C catalyst for 4h. The catalyst was removed by filtration and the filtrate evaporated to give the title compound (E21) (149mg).

mp 248-251°C

^1H NMR ($CDCl_3$) 250 MHz; δ: 1.35 (s, 6H), 1.68 (d, 2H), 2.50-2.67 (m, 3H), 2.75 (s, 3H), 2.99 (d, 2H), 3.17-3.26 (m, 2H), 3.58 (s, 2H), 3.61-3.71 (m, 2H), 4.37-4.49 (m, 1H), 6.89-6.97 (m, 1H), 7.06-7.20 (m, 2H), 7.88 (m, 1H).

M^+ 329

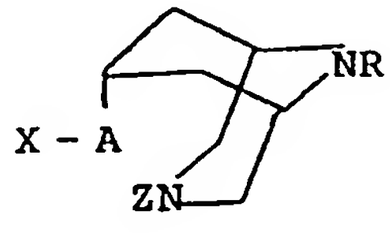
5-HT_3 Receptor Antagonist Activity

Compounds are evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

Male rats 250-350g, are anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate are recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6µg/kg) is given repeatedly by the intravenous route and changes in heart rate quantified. Compounds are given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the control response (ED_{50}) is then determined.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

X is a phenyl group or a monocyclic 5 or 6 membered heteroaryl group, either of which group is optionally fused to a saturated or unsaturated 5-7 membered carbocyclic or heterocyclic ring;

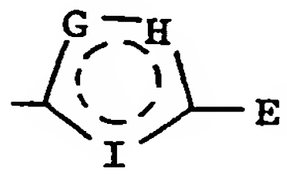
A is a linking moiety;

Z is C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl, naphthyl, phenyl C_{1-4} alkyl or naphthyl C_{1-4} alkyl wherein a phenyl or naphthyl moiety is optionally substituted by one or more of halo, C_{1-6} alkoxy or C_{1-6} alkyl;

R is hydrogen or methyl;

having 5-HT_3 receptor antagonist activity.

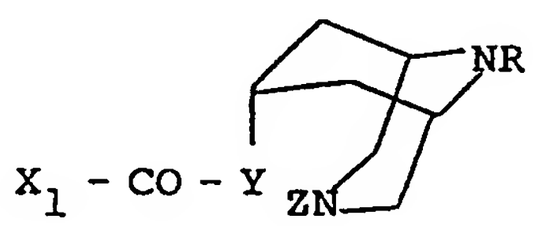
2. A compound according to claim 1 wherein A is CONH, NHCONH, CONHCONH or a group of structure (j):



(j)

wherein the dotted circle represents two double bonds in any position in the 5 membered ring; two of G, H and I are selected from oxygen, sulphur, nitrogen and carbon and the other is oxygen, sulphur or nitrogen; and E is a bond or C_{1-5} alkylene optionally substituted by phenyl or hydroxy.

3. A compound according to claim 1, of formula (IA), or a pharmaceutically acceptable salt thereof:

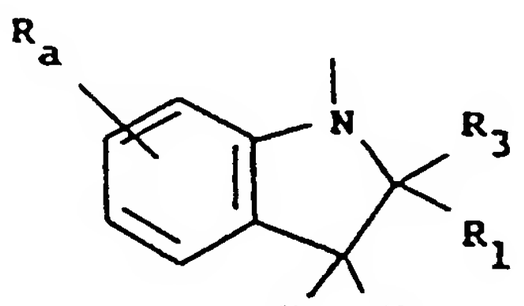


(IA)

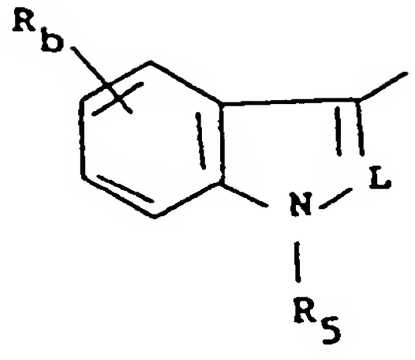
wherein

Y is NH or O (or is joined to R_{10} as defined below);

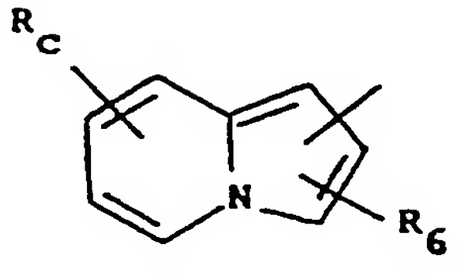
X_1 is a group of formula (a), (b), (c), (d), (e), (f), or (g) or (h):



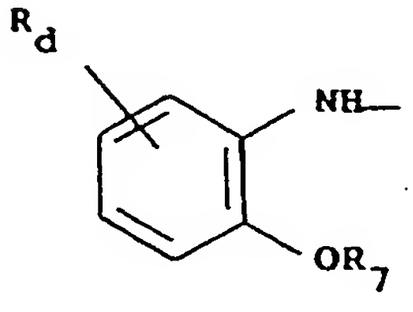
(a)



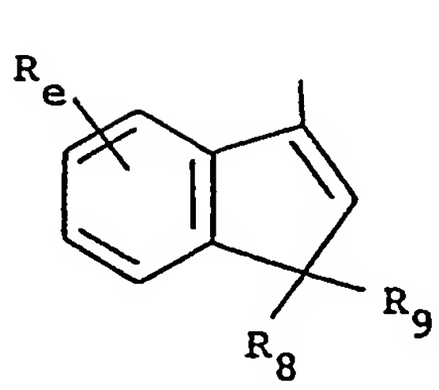
(b)



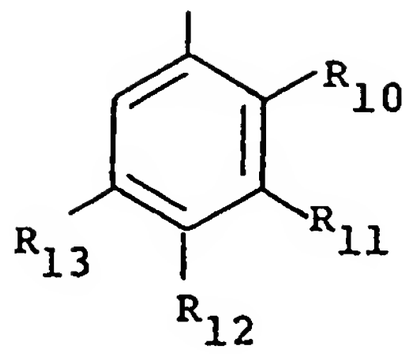
(c)



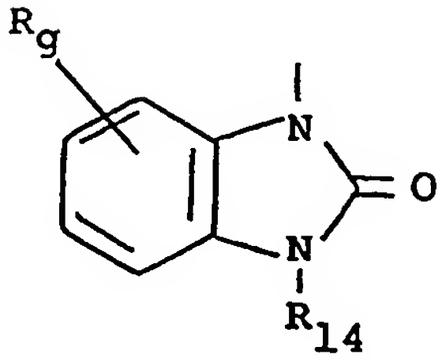
(d)



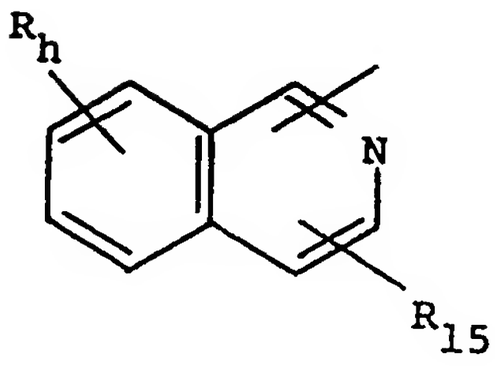
(e)



(f)



(g)



(h)

wherein

R_a to R_e and R_g to R_h are selected from hydrogen, halogen or hydroxy;

R_1 is hydrogen and R_2 is hydrogen or C_{1-4} alkyl; or

R_1 and R_2 together are a bond;

R_3 to R_7 are independently hydrogen or C_{1-6} alkyl; and

R_4 together with R_2 may be C_{2-7} polymethylene or C_{2-6} polymethylene interrupted by an -O- linkage when R_1 is hydrogen;

R_8 and R_9 are independently selected from hydrogen or

C_{1-6} alkyl or R_8 and R_9 together are C_{2-6} polymethylene or C_{2-5} polymethylene interrupted by an -O- linkage;

either R_{10} is hydrogen, C_{1-6} alkoxy, C_{3-8} cycloalkyloxy or C_{3-8} cycloalkyl C_{1-4} alkyloxy; or R_{10} is joined to Y so that Y-R_{10} is N-B=N where B is N or CH; and

R_{11} is hydrogen, halo, C_{1-6} alkoxy or C_{1-6} alkyl; or

R_{10} and R_{11} are joined to form -OCH($R_{15}R_{16}$)-E- wherein E is $(CH_2)_n$ or $NR_{17}CO(CH_2)m$ wherein n is 1 or 2 and m is 0 or 1 and R_{15}, R_{16} and R_{17} are independently selected from hydrogen or C_{1-6} alkyl;

R_{12} is hydrogen, C_{1-6} alkoxy or; amino optionally substituted by a C_{1-6} alkyl group, or R_{12} is alkanoylamino; and

R_{13} is halo, C_{1-6} alkyl, C_{1-6} alkoxy or C_{1-6} alkylthio;

R_{14} is hydrogen or C_{1-6} alkyl;

in formula (h):

CO-Y- is in the 1-position and either R_{15} is in the 3-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen, halogen, CF_3, C_{1-6} alkyl, C_{1-7} acyl, C_{1-7} acylamino, phenyl optionally substituted by one or two C_{1-6} alkyl, C_{1-6} alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C_{1-6} alkyl or C_{3-8} cycloalkyl groups or by C_{4-5} polymethylene or by phenyl, C_{1-6} alkylsulphonyl, C_{1-6} alkylsulphinyl, C_{1-6} alkoxy, C_{1-6} alkylthio, hydroxy or nitro; or

CO-Y- is in the 3-position and either R_{15} is in the 1-position and is hydrogen, C_{1-6} alkyl or C_{1-6} alkoxy, or R_{15} is in the 4-position and is hydrogen or C_{1-6} alkoxy;

L is CH or N; and

Z and R are as defined in claim 1.

4. A compound according to claim 3 wherein X is of sub-formula (a), one of R_1 and R_3 is hydrogen and R_2 and R_4

are both C_{1-6} alkyl groups or are joined to form C_{2-7} polymethylene.

5. A compound according to claim 3 wherein X is of sub-formula (b), and R_5 is hydrogen or a methyl or ethyl group.

6. A compound according to claim 3 wherein X is of sub-formula (d) and R_7 is methyl.

7. A compound according to claim 3 wherein X is of sub-formula (f) wherein R_{10} is methoxy, R_{12} is amino and R_{13} is chloro or bromo.

8. A compound according to any one of claims 1 to 7, wherein Z is benzyl, n- or iso-butyl, n- or iso-propyl, ethyl or methyl.

9. **endo**-4-Amino-5-chloro-2-methoxy-N-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)benzamide.

10. **endo**-4-Amino-5-chloro-2-methoxy-N-(3,9-dimethyl-3,9-diazabicyclo-[3.3.1]nonan-7-yl)benzamide.

11. **endo**-N-1-Methyl-3-indazolyl-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

12. **endo**-N-1-Methyl-3-indazolyl-(3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

13. **endo**-N-1-Methyl-3-indazolyl-(9-methyl-3-^{n}propyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

14. **endo**-N-1-Methyl-3-indazolyl-(3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

15. endo-N-1-Methyl-3-indazolyl-(3-^{n}butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

16. endo-N-1-Methyl-3-indazolyl-(3-(1-naphthylmethyl)-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

17. endo-N-1-Methyl-3-indazolyl-(3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

18. endo-N-1-Methyl-3-indazolyl-(9-methyl-3-phenethyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

19. endo-N-1-Methyl-3-indazolyl-(3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

20. endo-N-3,3-Dimethylindolin-1-yl-(3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

21. endo-N-3,3-Dimethylindolin-1-yl-(3-isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

22. endo-N-3,3-Dimethylindolin-1-yl-(3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

23. endo-N-3,3-Dimethylindolin-1-yl-(3-ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

24. endo-N-3,3-Dimethylindolin-1-yl-(3-^{n}propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

25. endo-N-3,3-Dimethylindolin-1-yl-(3-^{n}butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

26. **endo**-N-3,3-Dimethylindolin-1-yl-(3-isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

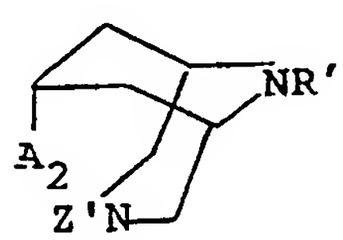
27. **endo**-N-3,3-Dimethylindolin-1-yl-(3-cyclohexylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl carboxamide hydrochloride.

28. **endo**-N-3,3-Dimethylindolin-1-yl-(9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-yl)carboxamide.

29. A pharmaceutically acceptable salt of a compound according to any one of claims 9 to 28.

30. A compound according to claim 1, substantially as described herein with reference to any one of the Examples.

31. A process for the preparation of a compound according to claim 1 which process comprises reacting a compound $X'-A_1$ with a compound of formula (II):



(II)

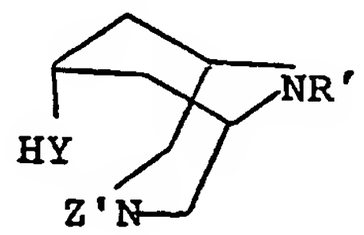
wherein A_1 and A_2 are moieties which react together, usually by an amide or ester coupling, or by condensation to form a heterocycle (j) as defined in claim 2, to form A as defined in claim 1; X' is X or a group convertible thereto and R'

and Z' are R and Z as defined in claim 1 or a hydrogenolysable protecting group; and thereafter as desired or necessary, converting X' to X, converting R'/Z', when other than R/Z, to R/Z, and optionally forming a pharmaceutically acceptable salt of the compound of formula (I).

32. A process for the preparation of a compound according to claim 3, which process comprises reacting a compound of formula (IV):

(IV)

with a compound of formula (V):



(V)

or a reactive derivative thereof, when Y is O;

wherein X_1' is X_1 or a group convertible thereto; Q_1 is a leaving group; R' is R as defined, or a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting X_1' to X_1, including any R_a, R_b, R_c, R_d, R_e, R_g, R_h or R_{10}, R_{11}, R_{12}, R_{13}, R_{14} or R_{15} group to another such group, converting R'/Z', when other than R/Z, to R/Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (IA).

33. An intermediate of formula (V) wherein R' is R and Z' is Z, as defined in claim 32.

34. **endo**-3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

35. **endo**-3-Isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]-nonan-7-amine.

36. **endo**-3-^{n}Propyl-9-methyl-3,9-diazabicyclo[3.3.1]-nonan-7-amine.

37. **endo**-3-Isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]-nonan-7-amine.

38. **endo**-3-^{n}Butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

39. **endo**-9-Methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

40. **endo**-9-Methyl-3-(1-naphthylmethyl)-3,9-diaza-bicyclo[3.3.1]nonan-7-amine.

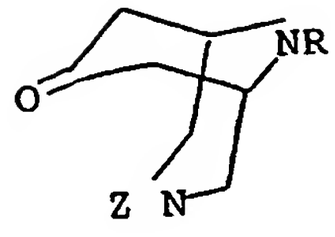
41. **exo/endo**-3,9-Dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

42. **endo**-3-Ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-amine.

43. **endo**-9-Methyl-3-(2-phenethyl)-3,9-diazabicyclo-[3.3.1]nonan-7-amine.

44. **endo**-3-Cyclohexylmethyl-9-methyl-3,9-diazabicyclo-[3.3.1]nonan-7-amine.

45. A compound of formula (III)'



(III)'

wherein Z and R are as defined in claim 1.

46. 3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

47. 3-Isopropyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

48. 3-n-Propyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

49. 3-Isobutyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

50. 3-^{n}Butyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

51. 9-Methyl-3-phenyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

52. 9-Methyl-3-(1-naphthylmethyl)-3,9-diazabicyclo-[3.3.1]nonan-7-one.

53. 3,9-Dimethyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

54. 3-Ethyl-9-methyl-3,9-diazabicyclo[3.3.1]nonan-7-one.

55. 9-Methyl-3-(2-phenethyl)-3,9-diazabicyclo[3.3.1]-nonan-7-one.

56. 3-Cyclohexylmethyl-9-methyl-3,9-diazabicyclo-[3.3.1]nonan-7-one.

57. A pharmaceutical composition comprising a compound according to any one of claims 1 to 30, and a pharmaceutically acceptable carrier.

58. A pharmaceutical composition for use in the treatment of pain, emesis, CNS disorders or gastrointestinal disorders comprising an effective amount of a compound according to claim 1, and a pharmaceutically acceptable carrier.

59. A compound according to any one of claims 1 to 30, for use as an active therapeutic substance.

60. A compound according to any one of claims 1 to 30, for use in the treatment of pain, emesis, CNS disorders or gastrointestinal disorders.

61. Use of a compound according to any one of claims 1 to 30, in the manufacture of a medicament for the treatment of pain, emesis, CNS disorders or gastrointestinal disorders.

62. A method of treatment of pain, emesis, CNS disorders or gastrointestinal disorders in mammals, which comprises the administration of an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01629

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 471/08 A 61 K 31/495 C 07 D 519/00 //
(C 07 D 471/08 C 07 D 241:00 C 07 D 221:00) (C 07 D 519/00, 471:00,471:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 471/00 C 07 D 519/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	GB,A,2193633 (SANDOZ) 17 February 1988, see claims	1,57

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
09-12-1991	23. 01. 92
International Searching Authority EUROPEAN PATENT OFFICE	**Signature of Authorized Officer** Danielle van der Haas

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 62 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple Inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9101629 SA 51590

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 13/01/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2193633	17-02-88	AU-A- 7194691	09-05-91
		AU-B- 610074	16-05-91
		AU-A- 7619087	04-02-88
		CH-A- 675072	31-08-90
		DE-A- 3724059	18-02-88
		FR-A- 2602142	05-02-88
		GB-A,B 2231264	14-11-90
		GB-A,B 2231265	14-11-90
		LU-A- 86950	02-02-88
		NL-A- 8701682	16-02-88
		SE-A- 8702980	28-04-88
		JP-A- 63041429	22-02-88